Research Article / *Araştırma Makalesi*

Ege Journal of Medicine / *Ege Tıp Dergisi* 2024; 63 (4): 586-594

Evaluation of lipid profile and statin therapy in patients with atrial fibrillation

Atriyal fibrilasyonlu hastalarda lipid profilinin ve statin tedavisinin değerlendirilmesi

Abdulrahman Naser[1] Yücel Uzun[1] Samet Sayılan[2] Oya Güven[3] Merve Demireller[4] Ahmet Ekmekçi[5]

[1] Kırklareli Training and Research Hospital, Department of Cardiology, Kırklareli, Türkiye

[2] Kırklareli University Medical School, Kırklareli Training and Research Hospital, Department of Internal Medicine, Kırklareli, Türkiye

[3] Kırklareli University Medical School, Kırklareli Training and Research Hospital, Emergency Department, Kırklareli, Türkiye

[4] Kırklareli Training and Research Hospital, Emergency Department, Kırklareli, Türkiye

[5] Bahçeşehir University, Department of Cardiology, Istanbul, Türkiye

ABSTRACT

Aim: Dyslipidemia is a modifiable risk factor of atrial fibrillation (AF). However, the majority of patients either do not receive low-density lipoprotein cholesterol (LDL-C) lowering treatment or do not meet their LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) goal. We aimed to search whether patients with AF are being treated for dyslipidemia and/or are at target LDL-C and non-HDL-C levels if treated.

Materials and Methods: This cross-sectional analysis includes 675 AF patients and was performed between 20 May 2023 and 25 November 2023, in cardiology outpatient clinics of a tertiary hospital. The demographic and clinical features of the patients were recorded. Systemic coronary risk estimation-2 (SCORE2) and old person version algorithms were used for cardiovascular disease (CVD) risk estimation. Primary prevention (PP) group involved patients with low-to-moderate, high and very high CVD risk without established atherosclerotic cardiovascular disease (ASCVD) and secondary prevention (SP) group consisted of patients with established ASCVD.

Results: The mean age of the participants was 71.98± 9.01 and 54.5% (n=368) of patients were females. 207 (30.7%) of patients were paroxysmal AF, and 468 (69.3%) were permanent AF. Prevalence of dyslipidemia and hypertriglyceridemia were 364 (53.9%) and 248 (36.7%) respectively. 9 (1.3%) and 152 (22.5%) of patients were on fibrate and statin treatment respectively. Mean LDL-C and non-HDL-C were 107.81±35.97 and 135.42±41.19 and their target attainment rates were 62 (9.2%) and 107 (15.9%), respectively.

Conclusion: Control of dyslipidemia in patients with atrial fibrillation was severely poor and the most common cause was physician inertia.

Keywords: Atrial fibrillation, dyslipidemia, low-density lipoprotein cholesterol, statin therapy.

ÖZ

Amaç: *Dislipidemi, atriyal fibrilasyonun (AF) değiştirilebilir bir risk faktörüdür. Ancak hastaların büyük çoğunluğu ya düşük yoğunluklu lipoprotein kolesterol (LDL-C) düşürücü tedavi almıyor ya da LDL-C ve yüksek yoğunluklu olmayan lipoprotein kolesterol (non-HDL-C) hedeflerine ulaşamıyor. AF'li hastaların dislipidemi için tedavi edilip edilmediğini ve/veya tedavi edilirlerse hedef LDL-C ve non-HDL-C düzeylerinde olup olmadıklarını araştırmayı amaçladık.*

Corresponding author: Abdulrahman Naser
Kırklareli Training and Research Hospital, Department of Cardiology, Kırklareli, Türkiye
E-mail: *abdulrahman_naser@hotmail.com*
Application date: 24.01.2024 Accepted: 05.09.2024

Gereç ve Yöntem: *Bu kesitsel analiz 675 AF hastasını içermektedir ve 20 Mayıs 2023 ile 25 Kasım 2023 tarihleri arasında üçüncü basamak bir hastanenin kardiyoloji polikliniklerinde gerçekleştirildi. Hastaların demografik ve klinik özellikleri kaydedildi. Kardiyovasküler hastalık (CVD) risk tahmini için sistemik koroner risk tahmini-2 (SCORE2) ve yaşlı kişi versiyonu algoritmaları kullanıldı. Birincil koruma (PP) grubu, belirlenmiş aterosklerotik kardiyovasküler hastalığı (ASCVD) olmayan düşük-orta, yüksek ve çok yüksek CVD riski olan hastaları içermektedir ve ikincil önleme (SP) grubu, belirlenmiş ASCVD'si olan hastalardan oluşmaktadır.*

Bulgular: *Katılımcıların yaş ortalaması 71,98± 9,01 olup hastaların %54,5'i (n=368) kadındı. Hastaların 207'si (%30,7) paroksismal AF, 468'i (%69,3) kalıcı AF idi. Dislipidemi ve hipertrigliseridemi prevalansı sırasıyla 364 (%53,9) ve 248 (%36,7) idi. Hastaların 9'u (%1,3) fibrat, 152'si (%22,5) ise statin tedavisi görüyordu. Ortalama LDL-C ve non-HDL-C sırasıyla 107,81±35,97 ve 135,42±41,19 olup, hedeflenen oranlara ulaşma oranları sırasıyla 62 (%9,2) ve 107 (%15,9) idi.*

Sonuç: *Atriyal fibrilasyonu olan hastalarda dislipideminin kontrolü oldukça zayıftı ve en yaygın neden doktor ihmaliydi.*

Anahtar Sözcükler: *Atriyal fibrilasyon, dislipidemi, düşük yoğunluklu lipoprotein kolesterol, statin tedavisi.*

INTRODUCTION

Atrial fibrillation is the most common cardiac arrhythmia disease, affecting more than 33 million people worldwide and is a significant cause of morbidity and mortality as it increases the likelihood of stroke and heart failure (1).

AF is a complex disease that develops as a result of the interaction of genetic and environmental factors. Several risk factors and comorbidities have been identified that can predispose to the development and progression of AF. These risk factors can be classified into non-modifiable (age and genetics), partially modifiable (coronary artery disease, heart failure, valvular heart disease, and chronic obstructive pulmonary disease), and modifiable (hypertension, diabetes, obesity, obstructive sleep apnea, alcohol, dyslipidemia, physical activity, and smoking) (1).

Although the clinical significance and pathophysiological mechanism of lipid level is controversial in the context of AF development. Dyslipidemia contributes to the development and progression of AF directly through the left atrial remodeling, and indirectly through the development of ASCVD (1-3). In addition, dyslipidemia is a clinical risk factor for stroke in patients with AF (1, 3).

Lipid-lowering therapy, especially statins, has been shown to have beneficial effects on both AF and ASCVD (3,4). Statins can reduce the incidence and recurrence of AF by improving the lipid profile, stabilizing the atrial membrane potential, and exerting pleiotropic effects, such as anti-inflammatory, antioxidant, antithrombotic, and anti-fibrotic actions. Statins may also prevent and treat ASCVD by lowering LDL-C and non-HDL cholesterol levels, lipid-lowering therapy's primary and secondary targets (3-7).

However, despite the strong evidence and clear recommendations, the use and effectiveness of lipid-lowering therapy in AF patients are suboptimal. Many AF patients do not receive adequate lipid-lowering treatment or do not achieve their lipid goals. The reasons for this gap are multifactorial, including patient-related factors (such as low awareness, poor adherence, and intolerance), physician-related factors (such as low awareness and inertia), and health system-related factors (such as lack of guidelines, resources, and incentives) (8,9).

Our main aim in this assay is to try to raise awareness about the management of dyslipidemia, which is an important part of the multidisciplinary approach in AF patients. In this work, we evaluate the lipid profile and statin therapy in patients with AF, using real-life data from a tertiary hospital in Türkiye. We assessed the prevalence of dyslipidemia and hypertriglyceridemia, the rate of use and adherence of lipid-lowering therapy, the achievement of lipid goals, and the factors associated with these outcomes. Furthermore, we discuss the implications and limitations of our findings and suggest possible ways to improve the management of dyslipidemia in AF patients.

MATERIALS and METHODS

The study was approved by the local Research Ethics Committee (P202300024/19.05.2023) and conducted by the Declaration of Helsinki. Written consent was obtained from all subjects.

The present study is a cross-sectional analysis of 675 consecutive AF patients who were admitted to a cardiology outpatient clinic of a tertiary hospital between 20 May 2023 and 25 November 2023. Inclusion criteria were having a diagnosis of AF confirmed by electrocardiogram or Holter monitoring and having sufficient data to calculate a 10-year ASCVD risk score. Exclusion criteria included being under 40 years of age, and having

contraindications to statin therapy such as liver failure or cirrhosis.

AF type was classified as paroxysmal or permanent according to the relevant guideline (1). The comorbidities, such as hypertension, diabetes, coronary artery disease, and stroke, were defined according to the standard criteria. The smoking status was self-reported by the patients. Medications taken by patients including statin and oral anticoagulant therapy was also recorded.

The blood samples were taken from the patients after overnight fasting and analyzed for fasting blood glucose, HbA1c, total cholesterol, HDL-C, triglycerides, and creatinine levels using standardized biochemical methods. The LDL-C level was estimated using the Friedewald formula and the non-HDL-C level was calculated by subtracting the HDL-C level from the total cholesterol level. The Cockcroft-Gault equation was used to estimate the glomerular filtration rate.

Dyslipidemia was defined as having a fasting total cholesterol level> 240 mg/dL, or an LDL-C level> 160 mg/dL, or taking lipid-lowering drugs. Hypertriglyceridemia was defined as having a serum triglyceride level ≥ 150 mg/dL or taking lipid-lowering drugs. The lipid-lowering therapy, including statins and fibrates, was recorded. The intensity of statin therapy was classified as moderate or high according to the relevant guidelines (2, 3). No patient was taking ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors.

We used the Systematic Coronary Risk Estimation (SCORE) charts to estimate the 10-year risk of ASCVD in patients aged 40-69 years and the SCORE2-OP charts to estimate the risk in patients aged ≥70 years, according to the relevant guidelines (3). We used the high-risk countries versions of the charts, as Türkiye is considered a high-risk country for ASCVD (10, 11).

We divided the study sample into two groups: primary prevention (PP) group and secondary prevention (SP) group. The PP group included patients with low-to-moderate, high, and very high CVD risk without established ASCVD, and the SP group included patients with established ASCVD. The CVD risk categories were defined according to relevant guidelines (3) as follows:

Very high-risk: Patients with established CAD, PAD, stroke, or severe chronic kidney disease (eGFR<30mL/min/1.73m2), or diabetic patients with eGFR<45mL/min/1.73m2, or apparently healthy participants <50 years, 50-69 years, and ≥70 years of age with an estimated ASCVD risk score of ≥7.5%, ≥10%, and ≥15%, respectively.

High-risk: Patients with long-standing (>10 years) DM, or moderate chronic kidney disease (eGFR 45-59 mL/min/1.73m2), or apparently healthy participants <50 years, 50-69 years, and ≥70 years of age with an estimated ASCVD risk score of 2.5 to <7.5%, 5 to <10% and 7.5 to <15%, respectively.

Low-to-moderate risk: Apparently healthy participants <50 years, 50-69 years, and ≥70 years of age with an estimated ASCVD risk score of <2.5%, <5% and <7.5%, respectively.

The target LDL-C levels were determined as <100 mg/dL, <70 mg/dL, and <55 mg/dL, and the corresponding non-HDL-C levels were determined as <131 mg/dL, <100 mg/dL, and <85 mg/dL for low-to-moderate, high, and very high CVD risk categories, respectively.

Patients were questioned whether their cholesterol levels were high, whether they knew their cholesterol levels, whether they took lipid-lowering medication, and whether they thought taking long-term cholesterol medication caused diabetes, dementia or cancer and why they not receiving cholesterol medication.

RESULTS

We included 675 AF patients (207 (30.7%) with paroxysmal AF and 468 (69.3%) with permanent AF, mean age 71.98 ± 9.01 years, 54.5% (n=368) females) in the study. Of these, 457 (67.7%) were in the PP group and 218 (32.3%) were in the SP group. According to the 2021 ESC-CVD prevention guideline, 46 (6.8%), 238 (35.3%), and 173 (25.6%) of the PP group had low-to-moderate, high, and very high CVD risk, respectively.

Table-1 shows the demographic and clinical characteristics and medication data of the study population. The number of women was significantly higher in each category of the PP group and lower in the SP group. The median age in the low-to-moderate CVD risk category was significantly lower than the other categories. There was no significant difference between the groups in terms of hypertension, hypothyroidism, COPD, smoking, and AF type (paroxysmal vs. permanent). As expected, ASCVD such as CAD, PAD, and stroke was only present in the SP group. Dyslipidemia was observed in 364 (53.9%) of the patients, and it was significantly more common in the SP group than the PP group. The only medications that showed a significant difference between the groups were antidiabetic drugs, statins, and ACE-I/ARBs. 152 (22.5%) patients were on statin treatment, of whom 119 (78.3%) were on moderate-intensity statin and 33 (21.7%) on high-intensity statin. Only 9 (1.3%) patients were on fibrate treatment. No patient was on ezetimibe or PCSK9 inhibitor or a combination of these molecules with statins. The post hoc analysis of the intergroup significant variables is given in detail in Supplementary Table-1.

Table-1. Data on demographic and clinical characteristics and medications of patients.

Variables	Total study population	Primary prevention			Secondary prevention	P
		Low-to-moderate CVD risk n:46 (6.8%)	High CVD risk n:238 (35.3%)	Very high CVD risk without established ASCVD n:173 (25.6)	Very high CVD risk with established ASCVD n:218 (32.3)	
Gender (F) n, (%)	368 (54.5)	33 (71.7)	146 (61.3)	89 (51.4)	100 (45.9)	0.001
Age (years), ±SD	71.98±9.01	61.59±6.32	73.74±8.91	72.06±7.87	72.20±9.05	<0.001
AF type						
• Paroxysmal AF	207 (30.7)	11 (23.9)	77 (32.4)	57 (35.8)	92 (26.1)	0.134
• Permanent AF	468 (69.3)	35 (76.1)	161 (67.6)	161 (64.2)	111 (73.9)	
CAD n, (%)	145 (21.5)	0 (0)	0 (0)	0 (0)	145 (66.5)	<0.001
PAD n, (%)	13 (1.9)	0 (0)	0 (0)	0 (0)	13 (6)	<0.001
Stroke n, (%)	95 (14.1)	0 (0)	0 (0)	0 (0)	95 (43.6)	<0.001
HT n, (%)	522 (77.3)	36 (5.3)	184 (27.3)	130 (19.3)	172 (25.5)	0.845
DM n, (%)	311 (46.1)	38 (82.6)	129 (54.2)	43 (24.9)	101 (46.3)	<0.001
Hypothyroidism n, (%)	62 (9.2)	8 (17.4)	22 (9.2)	12 (6.9)	20 (9.2)	0.190
COPD n, (%)	41 (6.1)	1 (2.2)	19 (8)	8 (4.6)	13 (6)	0.335
Dyslipidemia n, (%)	364 (53.9)	26 (56.5)	116 (48.7)	79 (45.7)	143 (65.6)	<0.001
Hypertriglyceridemia	248 (36.7)	24 (52.2)	84 (35.3)	57 (32.9)	83 (38.1)	0.104
Smoking n, (%)	236 (35)	16 (34.8)	80 (33.6)	68 (39.3)	72 (33)	0.575
Beta-blockers n, (%)	479 (71)	33 (71.7)	164 (68.9)	116 (67.1)	166 (76.1)	0.201
OADs n, (%)	226 (33.5)	32 (69.6)	104 (43.7)	0 (0)	90 (41.3)	<0.001
Insulin n, (%)	54 (8)	4 (8.7)	24 (10.1)	0 (0)	26 (11.9)	<0.001
ACEI/ARB n, (%)	437 (64.7)	27 (65.2)	154 (64.7)	97 (56.1)	156 (71.6)	0.017
CCB n, (%)	300 (44.4)	16 (34.8)	105 (44.1)	72 (41.6)	107 (49.1)	0.240
Digoxin n, (%)	126 (18.7)	14 (30.4)	46 (19.3)	30 (17.3)	36 (16.5)	0.163
Amiodarone n, (%)	38 (5.6)	6 (13)	14 (5.9)	7 (4)	11 (5)	0.125
Fibrate n, (%)	9 (1.3)	1 (2.2)	5 (2.1)	0 (0)	3 (1.4)	0.301
Statins n, (%)	152 (22.5)	4 (8.7)	42 (17.6)	20 (11.6)	86 (39.4)	<0.001
Statins intensity						
• High intensity statins n, (%)	33 (4.9)	2 (50)	5 (11.9)	7 (35)	19 (22.1)	0.096
• Moderate intensity statins n, (%)	119 (17.6)	2 (50)	37 (88.1)	13 (65)	67 (77.9)	
OACs						
• NOACs n, (%)	581 (86.1)	39 (84.8)	210 (88.2)	150 (86.7)	182 (83.5)	0.519
• Warfarin n, (%)	94 (13.9)	7 (15.2)	28 (11.8)	23 (13.3)	36 (16.5)	

ACEI: angiotensin-converting enzyme inhibitor, AF: atrial fibrillation, ARB: angiotensin receptor blocker, ASCVD: atherosclerotic cardiovascular disease, CAD: coronary artery disease, CCB: calcium channel blocker, COPD: chronic obstructive pulmonary disease, CVD: cardiovascular disease, DM: diabetes mellitus, F: female, HT: hypertension, NOAC: non-vitamin K anticoagulant, OAD: oral antidiabetic, PAD: peripheral artery disease, SD: standard deviation.

Table-2 shows the physical examination and laboratory data of the patients according to the ASCVD risk categories. There was no significant difference in BMI between the groups, but there was a significant difference in height and weight between the groups. SBP was not significantly different between the groups, but DBP and HR were significantly different between the groups. FG and HbA1c levels were also significantly different between the groups. Except for triglycerides, the lipid profile was significantly different between the groups. The lipid parameters were generally above the desired limits; the mean LDL-C and non-HDL-C levels were higher than the target levels recommended by the 2021 ESC-CVD prevention guidelines. Moreover, the rates of achieving both LDL-C and non-HDL-C targets were very low in all categories. Only 54 (8%) of the patients had the guideline-recommended target LDL-C level. In contrast, 621 (92%) patients were out of target LDL-C. The patients without established ASCVD

but with very high CVD risk had the highest LDL-C level and the highest percentage of LDL-C out of the target. The mean GFR was significantly different between the groups, as well. The mean CRP level in the SP group was not significantly different from the PP group with very high CVD risk, but it was significantly higher than the PP group with low-to-moderate and high CVD risk. The detailed intergroup significant differences are presented in Supplementary Table-1.

Table-3 shows the lipid profile in patients on statin treatment. The mean LDL-C and non-HDL-C levels of these patients were 92.94±39.93 mg/dL and 121.59 ± 46.33 mg/dL, respectively. In this group, only 25 (16.4%) and 42 (27.65%) patients achieved their target LDL-C and non-HDL-C levels, respectively, according to the guideline. As seen, patients in all categories were inadequately protected in terms of high LDL-C and non-HDL-C levels.

Figure-1 illustrates the reasons for patients not receiving statin treatment. 77.5% (n=523) of patients were not on statin treatment. The most common reason was physician inertia, which accounted for 56.79% of cases (n=297). The second most common reason was the failure to meet the conditions for the statins to be reimbursed by the social security system, which affected 38.62% of cases (n=202). The least common reason for discontinuing treatment was patient-related factors in 4.59% of cases (n=24), of these 24 cases, 9 discontinued statin therapy due to misinformation in the media, 5 due to side effects, 6 due to the advice of non-cardiologists, and 4 due to polypharmacy.

Table-2. Physical examination and laboratory data of patients with AF according to atherosclerotic cardiovascular disease risk categories.

Variables	Total study population	Primary prevention		Secondary prevention	P
		Low-to-moderate CVD risk n:46 (6.8%)	High CVD risk n:238 (35.3%)	Very high CVD risk without established ASCVD n:173 (25.6)	Very high CVD risk with established ASCVD n:218 (32.3)	
Hight (cm)	163 (12)	160 (10)	161.50 (12.25)	165 (12)	165 (12)	0.009
Weight (kg)	80 (18)	75 (19.75)	78 (19.25)	82 (15)	80 (18)	0.030
BMI (kg/m^2)	29.75 (6.71)	29.87 (8.31)	29.36 (6.48)	30.06 (7.58)	29.76 (6.18)	0.835
SBP (mmHg)	135 (25)	130 (22.50)	130 (20.50)	140 (29.50)	140 (20.50)	0.244
DBP (mmHg)	80 (20)	75 (21.25)	80 (15)	80 (20)	80 (15)	0.019
HR (beats/minute)	81±16	84.11±15.67	82.74±17.93	79.09±16.41	79.40±14.76	0.035
FG (mg/dL)	109 (37)	129 (56)	112 (39)	101 (19)	112.50 (52.50)	<0.001
HBA1c (%)	6 (1.07)	6.73 (1.79)	6.2 (1.26)	5.74 (0.40)	6.13 (1.52)	<0.001
TC (mg/dL), ±SD	183±42.55	187.07±37.42	185.21±40.12	193.17±42.73	173.04±44.02	<0.001
HDL-C (mg/dL)	46 (17)	45 (28.3)	46 (10.1)	49 (3.5)	45 (8.7)	0.019
LDL-C (mg/dL)	107.81±35.97	112.35±29.42	109.48±33.18	117.12±37.54	97.64±36.59	<0.001
LDL-C goal attainment	62 (9.2)	13 (1.3)	24 (3.6)	6 (0.9)	19 (2.8)	<0.001
Non-HDL-C (mg/dL)	135.42±41.19	142.59±32.68	137.09±38.37	143.09±43.24	126.02±42.53	<0.001
Non-HDLC goal attainment	107 (15.9)	16 (34.8)	45 (18.9)	12 (6.9)	34 (15.6)	<0.001
Both LDL-C and non-HDL-C goal attainment	52 (7.7)	10 (21.7)	23 (9.7)	4 (2.3)	15 (6.9)	<0.001
Triglyceride (mg/dL)	125 (87)	150.50 (95)	124.50 (89)	124 (81.50)	123.50 (85.50)	0.101
CRP (mg/dL)	7.54±6.51	5.39±3.09	6.66±6.15	8.13±6.40	8.47±7.28	0.002
Creatinine (mg/dL)	0.94 (0.39)	0.92 (1.22)	0.94 (0.39)	0.92 (0.53)	0.95 (0.32)	0.848
GFR (ml/minute)	84.06±33.74	99.79±36.09	80.07±31.69	84.42±36.82	84.81±32.01	0.004

ASCVD: atherosclerotic cardiovascular disease, BMI: body mass index, CRP: C-reactive protein, CVD: cardiovascular disease, DBP: diastolic blood pressure, FG: fasting glucose, GFR: glomerular filtration rate, HBA1c: hemoglobin-A1c, HDL-C: high-density lipoprotein cholesterol, HR: heart rate, LDL-C: low-density lipoprotein cholesterol, SBP: systolic blood pressure, TC: total cholesterol.

Table-3. Distribution of the lipid profile in patients using statin treatment.

Variables	Total	Primary prevention		Secondary prevention		P
		Low-to-moderate CVD risk n:4 (%)	High CVD risk n:42 (%)	Very high CVD risk without established ASCVD n:20 (%)	Very high CVD risk with established ASCVD n:86 (%)	
TC (mg/dL), ±SD	168.40±80.19	145.50±63.29	180.51±50.17	180.20±56.24	160.80±43.83	0.106
HDL-C (mg/dL)	45 (19)	48.50 (20.50)	43 (24.75)	45.50 (17.50)	45 (17.50)	0.891
LDL-C (mg/dL)	92.94±39.93	85.5±14.20	102.48±39.62	103.85±49.51	86.14±37.24	0.083
LDL-C goal attainment n, (%)	25 (16.4)	3 (75)	8 (19)	2 (10)	12 (14)	0.011
Non-HDL-C (mg/dL)	121.59±46.33	117.25±30.67	132.08±46.70	133.85±57.65	113.82±42.82	0.180
Non-HDLC goal attainment n, (%)	42 (27.6)	3 (75)	12 (28.6)	5 (25)	22 (25.6)	0.190
Both LDL-C and non-HDL-C goal attainment	21 (13.8)	2 (50)	8 (19)	2 (10)	9 (10.5)	0.093
Triglyceride (mg/dL)	123.5 (90.75)	166 (107.25)	130 (85.75)	126 (99)	115 (94.50)	0.437

ASCVD: atherosclerotic cardiovascular disease, CVD: cardiovascular disease, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol.

Supplementary Table-1. Post hoc analysis of significantly different variables among groups.

Age	Low-to-moderate CVD risk - High CVD risk	<0.001
	Low-to-moderate CVD risk - Very high CVD risk without established ASCVD	<0.001
	Low-to-moderate CVD risk - Very high CVD risk with established ASCVD	<0.001
Heart rate	High CVD risk - Very high CVD risk with established ASCVD	0.030
	High CVD risk - Very high CVD risk without established ASCVD	0.026
Hight	High CVD risk - Very high CVD risk without established ASCVD	0.033
Weight	High CVD risk- Very high CVD risk without established ASCVD	0.023
Diastolic blood pressure	High CVD risk - Very high CVD risk without established ASCVD	0.043
Glomerular filtration rate	Low-to-moderate CVD risk - Very high CVD risk with established ASCVD	0.036
	Low-to-moderate CVD risk - Very high CVD risk without established ASCVD	0.035
	Low-to-moderate CVD risk – High CVD risk	0.002
C-reactive protein	Very high CVD risk with established ASCVD - Low-to-moderate CVD risk	0.020
	Very high CVD risk with established ASCVD - High CVD risk	0.018
High-density lipoprotein cholesterol	Very high CVD risk with established ASCVD - Very high CVD risk without established ASCVD	0.018
Fasting glucose	Very high CVD risk without established ASCVD - Very high CVD risk with established ASCVD	<0.001
	Very high CVD risk without established ASCVD – High CVD risk	<0.001
	Very high CVD risk without established ASCVD – Low-to-moderate CVD risk	<0.001
Hemoglobin-A1c	Very high CVD risk without established ASCVD - Very high CVD risk with established ASCVD	<0.001
	Very high CVD risk without established ASCVD – High CVD risk	<0.001
	Very high CVD risk without established ASCVD -Low-to-moderate CVD risk	<0.001
	Very high CVD risk with established ASCVD – Low-to-moderate CVD risk	0.042
	High CVD risk -low-to-moderate CVD risk	0.043
Total cholesterol	Very high CVD risk with established ASCVD - Very high CVD risk without established ASCVD	<0.001
	Very high CVD risk with established ASCVD - High CVD risk	0.012
Low-density lipoprotein cholesterol	Very high CVD risk with established ASCVD - Very high CVD risk without established ASCVD	<0.001
	Very high CVD risk with established ASCVD - High CVD risk	0.002
Non-high-density lipoprotein cholesterol	Very high CVD risk with established ASCVD - Very high CVD risk without established ASCVD	<0.001
	Very high CVD risk with established ASCVD - High CVD risk	0.023

ASCVD: atherosclerotic cardiovascular disease, CVD: cardiovascular disease.

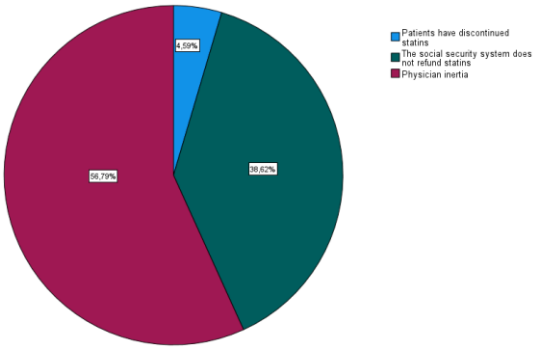

Figure-1. The reasons for patients not receiving statin treatment.

DISCUSSION

Our main aim in this study is to try to raise awareness about the management of dyslipidemia, which is an important part of the multidisciplinary approach in AF patients**.** We evaluate the lipid profile and statin therapy in patients with AF, using real-life data from a tertiary hospital. We found that dyslipidemia and hypertriglyceridemia were common in AF patients, but the use and effectiveness of lipid-lowering therapy were very low. Only 23.6% of the patients were on lipid-lowering therapy, mostly statins, and only 9.2% and 15.9% of the patients achieved their target LDL-C and non-HDL-C levels, respectively. The main reason for not receiving statins was physician inertia.

Dyslipidemias, primarily hypercholesterolemia and hypertriglyceridemia are independent and strong predictors of cardiovascular events. Additionally common in the general population and AF patients in Türkiye (12-14). The prevalence of hypercholesterolemia defined as a LDL cholesterol >130 and/or ≥130 mg/dL, is reported as 29.1% in the general population, 30.2% in females, and 27.8% in males. The prevalence of hypertriglyceridemia (>150 mg/dL) is reported as 36.5% in general, 32.0% in females and 41.3% in males (12). Our results are in consistence with previously published works that have reported a high prevalence of dyslipidemia and hypertriglyceridemia in AF patients, ranging from 30% to 50% (12, 13). Considering the results of the present analysis and a recent meta-analysis on the prevalence of dyslipidemia and lipid values in Türkiye (12), it appears that the frequency of dyslipidemia in AF patients is more common than in the general population.

Dyslipidemia is a modifiable risk factor for AF, as it can induce atrial remodeling and inflammation, and increase the risk of stroke and mortality (15). However, the relationship of lipid levels with the risk of AF development s controversial, some papers have suggested a paradoxical inverse relationship between cholesterol levels and AF incidence (13, 14, 16). This may be due to confounding factors, such as age, sex, ethnicity, and metabolic profile, and does not imply a causal relationship (15). The management of dyslipidemia is important for primary and secondary prevention of complications in AF patients.

Lipid-lowering therapy, especially statins, has been shown to have beneficial effects on both AF and ASCVD (1-3). Statins can reduce the occurrence and recurrence of AF by improving the lipid profile, stabilizing the atrial membrane potential, and exerting pleiotropic effects such as anti-inflammatory, antioxidant, antithrombotic, and anti-fibrotic actions (1-7,17). Statins are highly effective in preventing and treating ASCVD by significantly reducing LDL-C and non-HDL-C levels, which are lipid-lowering therapy's primary and secondary targets, respectively (2,3). However, despite the strong evidence and clear recommendations, in the present study the use and effectiveness of lipid-lowering therapy in AF patients are suboptimal, which is consistent with other studies that have reported low rates of statin prescription and target attainment in AF patients (18). LDL targets and risk stratification schemes in AF patients are similar to those in the general population (1, 2). The 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice recommend statin therapy for AF patients with high or very high CVD risk and suggest target LDL-C levels of <70 mg/dL and <55 mg/dL, respectively (2, 3). However, in our study, only 22.5% of the patients were on statin therapy, and only 8% of the patients achieved the guideline-recommended target LDL-C level. Moreover, no patient was on ezetimibe or PCSK9 inhibitor, which are effective adjunctive therapies for lowering LDL-C levels (3).

The underutilization and inefficacy of lipid-lowering therapy in AF patients have various factors, such as patient, physician, and health system factors (8, 9). In our study, the most common reason for not receiving statins was physician inertia, which may reflect a lack of awareness, reluctance to prescribe statins for AF patients. This may be due to the focus on anticoagulant therapy in AF patients, while little attention is paid to the multidisciplinary approach and treatment of comorbidities. Therefore, more education and guidance are needed for physicians who manage AF patients, to emphasize the importance and benefits of lipid-

lowering therapy for AF prevention and treatment.

Our study is one of the few studies that have evaluated the lipid profile and statin therapy in AF patients in Türkiye. Our findings are consistent with the AFTER study, which was a multicenter study that included 2242 AF patients with a mean age of 66.8 ± 12.3 years, female predominance, and permanent AF (18). According to the AFTER study, the average levels of TC, TG, HDL-C, and LDL-C were 177 ± 43, 136 ± 80, 42 ± 13, and 111 ± 34 mg/dL, respectively. The study also found that only 14.2% of patients received statin therapy (18). The most common comorbidity was hypertension. In our study, the lipid profile and the comorbidity pattern of our sample were very similar to the AFTER study, except that the statin usage rate was slightly higher in our study (22.5% vs. 14.2%).

However, our study also showed that the lipid control was poor in AF patients, especially in terms of LDL-C and non-HDL-C levels. According to clinical practice guidelines for preventing cardiovascular disease, only 9.2% and 15.9% of the patients achieved their target LDL-C and non-HDL-C levels (3). Moreover, the rate of reaching both LDL-C and non-HDL-C targets in the same person was even lower. These findings are in contrast with other studies that have reported higher rates of statin prescription and target attainment in AF patients in different geographical regions (19). The difference in the statin use and effectiveness may depend on various factors, such as income level, health care system, guideline adherence, and sample size.

Physician inertia is defined as the physicians' failure to initiate the treatment or intensify the dose or change the medication despite a higher level of a clinical parameter than levels established by guidelines. The main reason for physicians' inertia may be, inability to obtain adequate anamnesis and spare enough time to implement guideline recommendations for each patient, due to time constraints and large number of patients in daily outpatient clinics. Additionally, concerns about the negative side effects of statins and the thought that patients may be using statins may also cause physicians' inertia.

Reasons for patients to quit statins may include factors such as drug-related side effects, fear of adverse effect, psychological diseases, misinformation learned from the media, forgetting to take their medication, polypharmacy, problems in obtaining the drug, reaching the LDL-C target and resting the liver. It is important for physicians to provide adequate information to patients about the complications caused by high cholesterol, aiming for regular use of statins. Patients should know that the benefits of statins outweigh their potential side effects.

Turkey's social security institution reimburses statins in the following cases: in cases where the LDL level is above 190 mg/dl, or the LDL level is above 160 mg/dl with two additional risk factor from: hypertension, a family history of premature cardiovascular disease, and being 65 years of age or older, or in cases where the LDL level is above 130 mg/dl with there are three additional factors which are mentioned earlier, or in cases where the LDL level is above 70 mg/dl; Those with diabetes mellitus, acute coronary syndrome, previous stroke, coronary artery disease, peripheral artery disease, abdominal aortic aneurysm and carotid artery disease. The mentioned conditions do not fully meet the statin recommendations according to the SCORE category proposed by the ESC. As a possibility of improvement in statin provision, the social insurance institution in Turkey may implement the ESC recommendations. In addition, statin treatment could be initiated by primary care physicians.

Relatively large sample size, the use of real-life data from a tertiary hospital, and the use of the SCORE charts to estimate the CVD risk and categorize the patients according to the latest guidelines were the strengths of the present work. However, our study has several limitations; 1- The cross-sectional design that avoids causal inference. 2- The lack of the duration and adherence to lipid-lowering therapy. 3- The use of a single hospital records and self-reports, which can introduce measurement errors and bias.

CONCLUSION

Our study revealed that dyslipidemia and hypertriglyceridemia were common in AF patients, but the use and effectiveness of lipid-lowering therapy were very low. The main reason for not receiving statins was physician inertia. These findings suggest that there is a need for more education and guidance for physicians who manage AF patients, to improve the management of dyslipidemia and prevent AF and its complications.

Conflict of interest: The authors declared no conflict of interest.

References

1. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation, European Heart Journal (2020) 00, 1_126 doi:10.1093/eurheartj/ehaa612.
2. 2019 ESC-EAS Guidelines for the management of dyslipidemia. European Heart Journal (2019)00-,1-78, doi: :10.1093/eurheartj/ehz455
3. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. European Heart Journal (2021) 00, 1_111, doi:10.1093/eurheartj/ehab484
4. Flint AC, Conell C, Ren X et al. Statin adherence is associated with reduced recurrent stroke risk in patients with or without atrial fibrillation. Stroke. 2017;48:1788-94.
5. Li ZZ, Du X, Guo XY et al. Association Between Blood Lipid Profiles and Atrial Fibrillation: A Case-Control Study. Med Sci Monit. 20[18] Jun 9;24:3903-3908. doi: 10.12659/MSM.907580. PMID: 29885277; PMCID: PMC6024732
6. Fauchier L, Pierre B, de Labriolle A, Grimard C, Zannad N, Babuty D. Antiarrhythmic effect of statin therapy and atrial fibrillation. A meta-analysis of randomized controlled trials.J Am Coll Cardiol. 2008;51:828-35.10
7. Liu T, Li L, Korantzopoulos P, Liu E, Li G. Statin use and developmentof atrial fibrillation: a systematic review and meta-analysis ofrandomized clinical trials and observational studies. Int J Cardiol. 2008;126:160-70.
8. Başaran Ö, Doğan V, Mert KU et al. How did the updated 2019 European Society of Cardiology/European Atherosclerosis Society risk categorization for patients with diabetes affect the risk perception and lipid goals? A simulated analysis of real-life data from EPHESUS study. Anatol J Cardiol. 2023;27(2):78-87. DOI:10.14744/AnatolJCardiol.2022.2012.
9. Mert GÖ, Başaran Ö, Mert KU et al. The reasons of poor lipid target attainment for secondary prevention in real life practice: results from EPHESUS. Int J Clin Pract. 2019;73(9):1-9.
10. SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J 2021;42:24392454.
11. SCORE2-OP working group and ESC Cardiovascular risk collaboration. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. Eur Heart J 2021;42:24552467
12. Kayıkçıoğlu M, Tokgözoğlu L, Kılıçkap M, et al. Türkiye'de dislipidemi sıklığı ve lipit verileri: Kardiyovasküler risk faktörlerine yönelik epidemiyolojik çalışmaların sistematik derleme ve meta-analizi [Data on prevalence of dyslipidemia and lipid values in Turkey: Systematic review and meta-analysis of epidemiological studies on cardiovascular risk factors]. Turk Kardiyol Dern Ars. 2018 Oct;46(7):556-74. Turkish. doi: 10.5543/tkda.2018.23450. PMID: 30391985.
13. Hyun-Jung Lee, So-Ryoung Lee, Eue-Keun Choi, Kyung-Do Han, Seil Oh. Low cholesterol levels and high cholesterol variability were associated with a higher risk of AF development. (J Am Heart Assoc. 2019;8:e012771. DOI: 10.1161/JAHA.119.012771.)
14. Qi Jiang, Ling Yang, Ming-Long Chen, Fei Hua, Jian-Jun Li. Lipid Profile and Atrial Fibrillation: Is There Any Link?. Rev. Cardiovasc. Med. 2022, 23(8), 272. https://doi.org/10.31083/j.rcm2308272
15. Li F, Du X, He L et al. Relationship between serum lipid levels and ischemic stroke in patients with atrial fibrillation: a nested case–control study based on the China Atrial Fibrillation Registry. BMC Cardiovasc Disord. 21, 424 (2021). https://doi.org/10.1186/s12872-021-02237-6
16. Harrison SL, Lane DA, Banach M et al. Lipid levels, atrial fibrillation and the impact of age: Results from the LIPIDOGRAM2015 study. Atherosclerosis. 2020; 312: 16–22.
17. Fauchier L, Pierre B, de Labriolle A, Grimard C, Zannad N, Babuty D. Antiarrhythmic effect of statin therapy and atrial fibrillation. A metaanalysis of randomized controlled trials. J Am Coll Cardiol. 2008;51: 828-35.
18. Faruk Ertaş, Hasan Kaya, Zekeriya Kaya, Serkan Bulur, Nuri Köse, Mehmet Gül. Epidemiology of atrial fibrillation in Turkey: preliminary results of the multicenter AFTER∗ study. Türk Kardiyol Dern Arş- Arch Turk Soc Cardiol. 2013;41(2):99-104 doi: 10.5543/tkda.2013.18488
19. Hanna IR, Heeke B, Bush H et al. Lipid-lowering drug use is associated with reduced prevalence of atrial fibrillation in patients with left ventricular systolic dysfunction. Heart Rhythm. 2006 Aug;3(8):881-6. doi: 10.1016/j.hrthm.2006.05.010. Epub 2006 May 9. PMID: 16876733; PMCID: PMC3164215.